SERUM URIC ACID PROFILE IN 100 CASES OF STEMI

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CERTIFICATE

This is to certify that this dissertation entitled **"SERUM URIC ACID PROFILE IN 100 CASES OF STEMI"** is a bonafide record of work done by **Dr.S.RAJA** under my guidance and supervision in Tirunelveli Medical College Hospital during the period of his Post Graduate Study for M.D. (General Medicine) from 2007 – 2010.

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Finally with grace of almighty God and with the cooperation of the patients, I completed this study.

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1. INTRODUCTION

Patients with ischemic heart disease fall into two large groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina and patients with acute coronary syndromes (ACSs)[1,2]. The latter group, in turn, is composed of patients with acute myocardial infarction (MI) with ST-segment elevation on their presenting electrocardiogram and those with unstable angina and non-ST-segment elevation MI (UA/NSTEMI)[3,4].

The early (30-day) mortality rate from AMI is ~30%, with more than half of these deaths occurring before the stricken individual reaches the hospital[5]. Although the mortality rate after admission for AMI has declined by ~30% over the past two decades, approximately 1 of every 25 patients who survives the initial hospitalization dies in the first year after AMI. Mortality is approximately fourfold higher in elderly patients (over age 75) compared with younger patients[6,7].

Early Complications of STEMI include Ventricular dysfunction, Cardiogenic shock[8,9], Infarction related arrhythmias, thromboembolism , Left ventricular aneurysm[10], papillary muscle rupture, ventricular free wall rupture and ventricular septal rupture[13,14].

In clinical practice, there are many scoring systems[15] based on either clinical features or ECG changes are used for predicting the early complications following STEMI. KILLIP's classification[18], TIMI

scoring system[16,17] and PREDICT scoring system are few among them. There are certain biochemical substances are also found to be elevated in complicated cases of STEMI like HsCRP, NT-BNP[19] by various studies. Serum uric acid is one among them which is being under study in acute coronary syndromes as a prognostic predictor [20-25]. My study is mainly intended to find whether there is an association between hyperuricemia and early complications of STEMI or not.

2.AIMS AND OBJECTIVES

The Aims and Objectives of this study are:

1. To know the prevalence of Hyperuricemia in STEMI patients.
2. To know the significance of association of Hyperuricemia with other cardio vascular risk factors.
3. To know the association of Hyperuricemia with infarction pattern.
4. To know the significance of association of Hyperuricemia with early complications of STEMI.

3.REVIEW OF LITERATURE

Acute myocardial infarction with ST-segment elevation (**STEMI**) remains a major global public health issue. Despite advances in therapy, patients remain at risk for death, repeat myocardial infarction (MI), shock and heart failure (HF). Novel markers that predict those at risk are needed.

Study conducted by Justin A Ezekowitz and Jeffery A Bakal et al at University of Alberta, Edmonton, Canada among 903 STEMI patients revealed that NT-proBNP performed early and at 24 hrs provides important prognostic information for predicting negative outcomes i.e. shock, heart failure and death[19].

A wide variety of nonlipid biochemical markers have been suggested in an effort to better identify those individuals at an increased for complications of myocardial infarction., including markers of fibrinolytic and hemostatic function (tissue type plasminogen activator antigen, plasminogen activator inhibitor-1, fibrinogen, von Willibrand, D-dimer, thrombin-antithrombin III complex, and factors V, VII, and VIII), homocysteine, and markers of inflammation (high-sensitivity C-reactive protein (hsCRP), serum amyloid A, interleukins, adhesion molecules, heat shock proteins, and matrix metalloproteases,and Serum uric acid[26].

SERUM URIC ACID

An association between elevated levels of circulating uric acid and increased incidence of morbidity and mortality in acute coronary syndromes has been documented for many years. Since then, several studies are coming up supporting this issue.

Biochemistry and Physiology:

In humans, uric acid (2, 6, 8 – trihydroxy purine) is the major product of the catabolism of the purine nucleosides, adenosine and guanosine. Purines from catabolism of dietary nucleic acid are converted to uric acid directly[27].

The bulk of purine excreted as uric acid arise from degradation of endogenous nucleic acids. The daily synthesis rate of uric acid is approximately 400mg; dietary sources contributes another 300mg[27]. In men consuming a purine - free diet, the total body pool of exchangeable urate is estimated as 1200 mg.

In women it is estimated to be 600mg. By contrast patients with gouty arthritis and tissue deposition of urate may have urate pools as large as 18000 to 30000 mg[28]. Overproduction of uric acid may result from increased synthesis of purine precursors.

Synthetic Pathway of Uric acid:

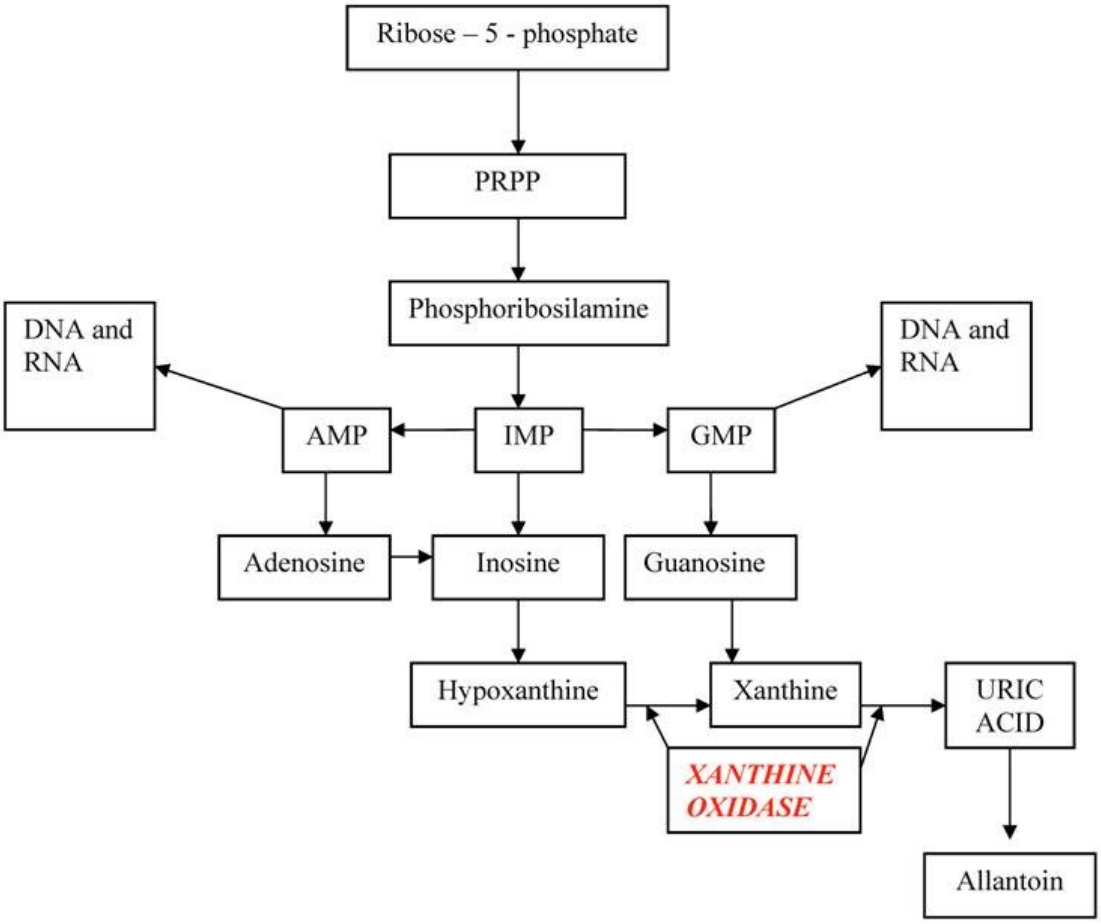

Fig 3.1 Synthetic Pathway of Uric Acid

Fate of Uric acid:

Lower primates and mammals other than humans carry purine metabolism one step further with the formation of allantoin from uric acid, a step mediated by uricase oxidoreductase[29]. In humans, approximately 75% of uric acid excreted is lost in the urine most of the remainder is secreted into the gastrointestinal tract, where it is degraded to attention and other compounds by bacterial enzymes[31,32].

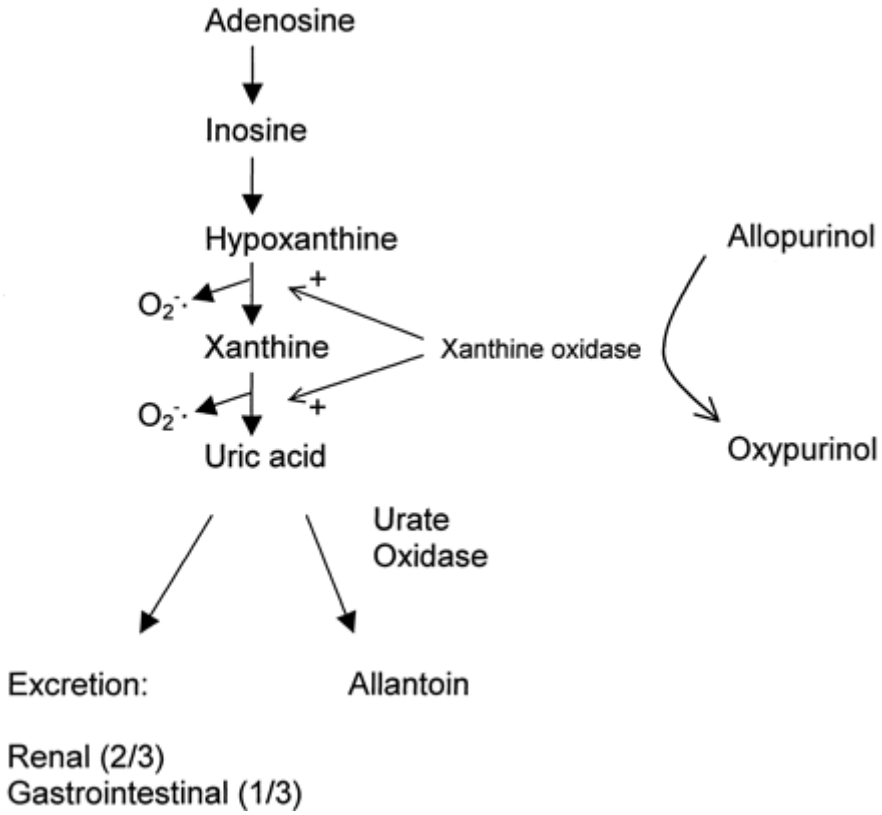

Fig 3.2 Fate of Uric Acid

Renal handling of uric acid[30]:

1.Glomerular filtration of virtually all the uric acid in capillary plasma entering the glomerulus.

2.Re-absorption in the proximal convoluted tubule of about 98% to 100% of filtered uric acid.

3.Subsequent secretion of uric acid into the lumen in the distal portion of the proximal tubule.

4.Further re-absorption in the distal tubule.

The net urinary excretion of uric acid is 6% to 12% of the amount filtered.

Major Causes of Hyperuricemia:

Increased formation → Primary:

- Idiopathic
- Inherited Metabolic disorder

Secondary:

- Excess dietary purine intake
- Increased nucleic acid turnover (leukemia, myeloma, radiotherapy, chemotherapy, trauma)
- Psoriasis
- Altered ATP metabolism
- Tissue hypoxia
- Pre- eclampsia
- Alcohol

Decreased Excretion → Primary:

- Idiopathic

Secondary:

- Acute/Chronic kidney disease
- Increased renal re-absorption
- Reduced secretion
- Lead poisoning
- Preeclampsia

- Low dose salicylates
- Thiazide diuretics
- Trisomy 21

Pathophysiology of raised SUA in Coronary artery diseases:

There is increasing evidence that strongly supports a direct pathophysiological role for the metabolic pathway leading to UA production in the failing circulation. In this regard, the two terminal steps in urate production are catalyzed by XO, which also produces a molecule of superoxide for each reaction5 XO is the product of the xanthine oxidoreductase gene that encodes XDH, an 150 Kda protein, which functions as a homodimer. XDH is converted to XO by proteolytic cleavage or sulfhydryl modification[33.]

The elevation in serum UA may reflect increased XO pathway activity and in turn the generation of superoxide and resultant oxidative stress via the XO system. XO is upregulated within the heart in both experimental and human heart failure[34]. Much had previously been made of the difficulty in identifying XO within the hearts of certain mammalian species, including humans; nevertheless, it is clear that XO, which is produced in highest abundance in the liver and gut, may circulate in the blood and adhere to endothelium in distant sites[35.]

Moreover, XO is expressed in cardiac myocytes, as shown by immunohistochemistry and may participate in intracrine signaling.From a functional standpoint, XO activity participates in both Mechanoenergetic uncoupling and vascular dysfunction in the failing circulation. Mechanoenergetic uncoupling is the process whereby cardiac energy consumption remains the same or increases while cardiac work falls dramatically, and is increasingly being perceived as a potential key lesion in the failing heart. Inhibition of XO with allopurinol restores depressed myocardial energetics toward normal, and this effect can be mimicked by the antioxidant ascorbate.

Furthermore, several recent studies have demonstrated that XO inhibition improves endothelial dysfunction in patients with congestive heart failure in association with reduction in circulating markers of oxidative stress, thereby providing evidence that XO inhibition reduces oxidant generation[36].

Beyond XO activity, recent experimental studies suggest that UA itself may have a role in cardiovascular and renal pathophysiology. This might seem surprising, as UA can function as an antioxidant, both by itself and by promoting superoxide dismutase activity and might therefore be considered potentially protective. However, UA potently stimulates vascular smooth muscle cell proliferation in vitro,an effect mediated by stimulation of mitogen-activated protein kinases,

cyclooxygenase-2, and platelet-derived growth factor[37].

Furthermore, rats with mild experimentally induced hyperuricemia develop intrarenal vascular disease with increased renin expression, systemic and glomerular hypertension, and renal injury in the absence of intrarenal crystal deposition.These hemodynamic and structural changes can be prevented if UA elevation is prevented by allopurinol[38].

Interaction of Xanthine Oxidase and Uric Acid With Nitric Oxide Pathways:

Both XO activity and UA may also affect cardiac and renal nitric oxide signaling, which exerts key cardiac and vascular effects[39]. The impact of XO inhibition to restore depressed myocardial energetics requires intact NO pathway activity.UA may also impair NO production directly, as suggested by the finding that UA infusion into forearm veins of humans attenuates acetylcholine-stimulated vasodilation[40].

Likewise, the hypertension associated with hyperuricemia in rats is associated with reduced expression of macula densa neuronal nitric oxide synthase (NOS) and can be partially reversed by the NOS substrate L-arginine[19]. This finding has interesting implications for cardiac function, as neuronal NOS plays a key role in modulating cardiac excitation-contraction coupling by facilitating sarcoplasmic reticulum calcium release.

Recent data suggest that uric acid is generated locally in the vessel wall by the action of xanthine oxidase. This enzyme, activated during ischemia- reperfusion by proteolytic conversion of xanthine dehydrogenase, catalyzes the oxidation of xanthine, thereby generating free radicals and uric acid.

Because of the potential role of ischemia -reperfusion in vascular disease, the effects of uric acid on rat aortic vascular smooth muscle cell (VSMC) growth was studied[41]. Uric acid stimulated VSMC DNA synthesis, as measured by [3H] thymidine incorporation, in a concentration-dependent manner with half-maximal activity at 150 PM. Neither uric acid precursors (xanthine and hypoxanthine) nor antioxidants (ascorbic acid, glutathione,a nd a-tocopherol) were mitogenic for VSMC. Uric acid was mitogenic for VSMC but not for fibroblasts or renal epithelial cells. The time course for uric acid stimulation of VSMC growth was slower than serum, suggesting induction of an autocrine growth mechanism.

Exposure of quiescent VSMC to uric acid stimulated accumulation of PDGF α-chain mRNA (>5-fold at 8 h) and secretion of PDGF- like material in conditioned medium[45,46].

Uric acid-induced [3H]thymidine incorporation was markedly inhibited by incubation with anti-PDGF α chain polyclonal antibodies. Thus uric acid stimulates VSMC growth via an autocrine mechanism involving PDGF α -chain[42].

These findings suggest that generation of uric acid during ischemia-reperfusion contributes to atherogenesis and intimal proliferation following arterial injury.

OTHER BIOMARKERS

High-Sensitivity C-Reactive Protein

Tillet and Francis in 1930 described a substance that was present in the sera of acutely ill patients and able to bind the cell wall C-polysaccharide of *Streptococcus pneumoniae* and agglutinate the organisms. In 1941 the substance was shown to be a protein and given the name *C-reactive protein (CRP).*

CRP was subsequently shown to be an acute phase reactant and important in the nonspecific host defense against inflammation, especially infection and is routinely monitored as an indication of infection and autoimmune diseases using methods having detecting limits of 3 to 8 mg/L

Chronic inflammation is an important component in the development and progression of atherosclerosis, and numerous epidemiological studies have demonstrated that increased serum CRP concentrations are positively associated with a risk of future coronary events, such as coronary artery disease or peripheral arterial disease[47]. It has also been shown to be predictive of future events in patients with acute coronary syndromes and in patients with stable angina and coronary artery stents.

In general, those individuals with baseline hsCRP values in the top quartile of the sample distribution are 2 to 3 times more likely to experience a future vascular event than those in the bottom quartile. The

association between hsCRP and future vascular events is linear and is independent of age, smoking, hypertension, dyslipidemia, and diabetes. For example, 8-year follow-up data from the Physicians' Health Study and the WHS showed that after adjustment for traditional risk factors, there was an increase in a future cardiovascular risk of 26% for men and 33% in women for each quintile increase in baseline hsCRP[48].

Since hsCRP values minimally correlate with lipid concentrations and lipid parameters account for <3% to 5% of the variance in hsCRP measurement, the measurement of hsCRP does not replace but instead complements the evaluation of lipids and other classical CHD risk factors in primary prevention settings[49].

Data from the WHS demonstrated that hsCRP adds prognostic information not only at all levels of the risk defined by current LDL cut points of the NCEP but also at all levels of the risk specified by the Framingham risk score algorithm.

Serum Homocysteine:

Numerous studies have suggested an association between elevated levels of circulating homocysteine and various vascular and cardiovascular disorders. In addition, tHcy levels also are related to birth defects, pregnancy complications, psychiatric disorders, and mental impairment in the elderly. Clinically the measurement of tHcy is considered important

(1) to diagnose homocystinuria,

(2) to identify individuals with ur at a risk of developing cobalamin or

folate deficiency, and

(3) to assess tHcy as a risk factor for cardiovascular disease (CVD) and

other disorders[50].

Serum Amyloid

Serum amyloid protein-A is an acute phase protein, and an apolipoprotein has often been used with hsCRP in cross sectional studies. It can be synergistic with hsCRP[51] but is much less commonly used. At present, there is no standardized assay and no reference interval studies or consistent assay validations.

sCD40 Ligand

sCD40 ligand is a transmembrane protein related to TNF. It has multiple prothrombotic and proatherogenic effects. What is usually measured is the soluble form of the receptor, which has been shown to be a predictor of events after acute presentations[52]. At present, there is no standardized assay and no reference intervals studies or consistent assay validations.

Cytokines

There are a variety of stimulatory and inhibitory interleukins (TNF, IL-1, IL-6, IL-8, IL-12, IL-18) that are thought to help mediate the elaboration of CRP and the development of atherosclerosis and acute events. These cytokines either stimulate or inhibit leukocytes, often through T-cell mediated processes , which are indigenous to atherogenesis[53]. In some studies, IL-6 is more prognostic than hsCRP. These cytokines often have inhibitors and/or binding proteins that modulate their effects. At present, there are no standardized assays and no normal range studies or consistent assay validations.

Myeloperoxidase

Myeloperoxidase is released when neutrophils aggregate and thus may indicate an active inflammatory response in blood vessels. It has been shown to be elevated chronically when chronic CAD is present[54]. It is increased when patients present with ACS. Initial prognostic studies were encouraging but were done without adequate consideration of other analytes and specifically cardiac troponin. Accordingly, additional studies are needed. At present, there is no standardized assay and no reference interval studies or consistent assay validations.

Phospholipase A2

Phospholipase A2 (Lp PLA2) is a phospholipase associated with LDL and is thought to be an inflammatory marker. It was previously known as platelet activating factor acetyl hydrolase (PAF). It is synthesized by monocytes and lymphocytes. It is thought to cleave oxidized lipids to induce lipid fragments that are more atherogenic and that increase endothelial adhesion. There is an FDA approved assay for this analyte with obligatory normal intervals. It has been shown to be predictive of events in a primary prevention cohort even when hsCRP is present in the model, suggesting it measures something different from the acute phase reactants associated with hsCRP[55].

Pregnancy Associated Plasma Protein A

Pregnancy associated plasma protein A (PAPP-A) is a metalloproteinase expressed when IGF is freed from inhibition. It is thought to be expressed in plaques that may be prone to rupture. The literature in this regard is mixed at present concerning its use[56]. At present, there is no standardized assay and no reference interval studies or consistent assay validations.

Oxidized LDL:

Oxidized LDL has been attributed a key role in the development of atherosclerosis. Several methods have been used to measure it, but they give potentially different data. Some have correlated malondialdehyde

LDL with the development of atherosclerosis and short-term events[57]. Direct identification with antibodies suggests that oxidized LDL may be released from vessels and co-localize with Lp(a) after acute events.

Placental Growth Factor

Placental growth factor is an angiogenic factor related to vascular endothelial growth factor (VEGF), which stimulates smooth muscle cells and macrophages. It also increases TNF and MCP-1. There is a novel assay for this analyte that is thought to provide additional prognostic information on patients who present with ACS.[58] At present, there is no standardized assay and no reference interval studies or consistent assay validations.

Matrix Metalloproteinases

Matrix metalloproteinases (MMP) can degrade the collagen matrix in either coronary artery or myocardium. They are integral to remodeling of the coronary artery and/or the heart after acute events. Elaboration of MMP 9, a gelatinase, is thought to be important in plaque destabilization and thus some have tried to measure it as a prognostic index[59]. Other MMPs participate in the elaboration of extracellular matrix in the heart. Many of the MMPs also have inhibitors (TIMPs) that modulate their effects. At present, there are no standardized assays and no normal range studies or consistent assay validations.

Monocyte Chemotactic Protein

Monocyte chemotactic protein (MCP-1) is a chemokine that is thought to be responsible for the recruitment of monocytes into atherosclerotic plaque. It has been reported to be elevated in patients with ACS and to have long-term predictive value[60]. However, at present, there is no standardized assay and no reference interval studies or consistent assay validations.

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNFa) is an inflammatory cytokine and interleukin that is involved in the genesis of sepsis, arthritis, and a variety of other inflammatory states . It also has hemodynamic effects and reduces ventricular performance. It is also a common signaling molecule. Assays for it or its receptor have been developed, but the failure of recent therapeutic trials has led to concern about how to properly interpret the high levels seen in patients with CHF and coronary heart disease[61]. At present, there are no standardized assays and no reference interval studies or consistent assay validations.

Tissue Plasminogen Activator Antigen

Tissue plasminogen activator antigen (t-PA antigen and activity) and plasminogen activator inhibitor 1 (PAH). t-PA is the body's physiological fibrinolytic activator. PAI-1 is its endogenous inhibitor and binds to t-PA. Inhibition of fibrinolysis has been suggested to be a reason

for recurrent infarction and the fact that maximal inhibition usually occurs in the early morning hours a reason for the circadian variability of AMI[62]. It may also be the reason why diabetics have such unstable disease since the growth factor properties of insulin stimulate increases in PAI-1. An accurate assessment of this system includes both and some assessment of the bound compared with free levels.

Secreted Platelet Granular Substances

Both platelet factor 4 (PF4) and beta thromboglobulin (BTG) are secreted when platelets aggregate. PF4 has a short half-life, is released by heparin, and is the cause of the antibodies that result in heparin-induced thrombocytopenia. BTG is not released by heparin and has a longer half-life. Both markers have been used to assess platelet aggregation[63]. BTG is by far the most reliable. At present, there are no standardized assays and no reference interval studies or consistent assay validations.

Isoprostanes

Isoprostanes are the end breakdown products of lipid peroxidation, and urinary levels have been used to assess the level of oxidative stress[64]. It is thought that oxidation of LDL is essential for the development of atherosclerosis and that HDL and other antioxidants work by antagonizing this oxidative stress. Urinary isoprostanes give one some summary assessment of this critical process. The most common ones measured are F_2-isoprostanes, but there are a large number of potential

ones to measure. It does appear that they will eventually be helpful in assessing oxidative stress.

Urinary Thromboxane

Urinary thromboxane is the end metabolite of thromboxane A2, which is a measure of platelet aggregation. Urinary levels are elevated in patients with unstable coronary disease in keeping with the known participation of platelets in the pathogenesis of CAD. It is difficult to measure, and collecting urine in acute situation is at times problematic.

Adhesion Molecules

Adhesion molecules are a wide variety of molecules that can potentially be measured as a way of assessing the adherence of leukocytes and/or platelets or other adhesive proteins to the endothelial matrix[65]. Some are receptors. Some of the examples include PECAM-1 (platelet-endothelial adhesion molecule 1), P-selectin, e-selectin, and VCAM-1 (vascular cell adhesion molecule 1). At times, the receptor itself is measured but often it is a soluble portion that circulates that is the ligand. At present, there are no standardized assays and no reference interval studies or consistent assay validations..

Ischemia Modified Albumin

Ischemia modified albumin (IMA), measured by the albumin cobalt binding test, has been approved by the FDA for its negative predictive value in concert with a normal ECG and a normal cardiac

troponin. This test relies on changes in the binding of cobalt to the albumin molecule when ischemia is present[66]. It requires additional validation of the meaning of a positive test before clinical use for ruling in ischemia.

Choline

Choline is released after stimulation by phospholipase D and has been touted as a test of prognosis in patients with chest discomfort.[67] At present, there is no standardized assay and no reference interval studies or consistent assay validations.

Unbound Free Fatty Acid

Unbound free fatty acid (uFFA) has also been touted as a marker of ischemia. Most fatty acid is bound and ischemia is thought to increase the small unbound fraction. Initial studies have reported mixed results[68]. At present, there is no standardized assay and no reference interval studies or consistent assay validations.

Nourin

Nourin I is a small protein released rapidly by "stressed myocytes." It induces changes in a variety of inflammatory cytokines and attracts neutrophils. Preliminary studies have been done attempting to validate its use[69]. At present, there is no standardized assay and-no reference interval studies or consistent assay validations.

4. MATERIALS AND METHODS

Study design:

This is a cross-sectional study.

Place of study:

This study was carried out in the Department of Medicine, Intensive Cardiac Care Unit, Tirunelveli Medical College Hospital.

Study population:

100 patients of STEMI who got admitted serially in ICCU.

Inclusion criteria:

1. Cases with STEMI who fulfilled the pre-requisites for thrombolysis and thrombolysed with streptokinase.
2. Both failed and successful thromolysed cases were included.

Exclusion criteria:

Patients with STEMI,

1. Not thrombolysed because of late presentation or patients having contra-indication for streptokinase use.
2. With renal failure
3. On drugs like diuretics, pyrazinamide

Study method:

This study was approved by the Ethical Committee of our institute.

Patients were selected for study according to the inclusion and exclusion criteria, mentioned above . Detailed history regarding smoking,

alcoholism, diabetes mellitus, hypertension, Drug intake was enquired. Vital signs, waist/Hip ratio, 15 lead-ECG findings were noted. Blood sugar values, Fasting lipid profile and Fasting Serum uric acid were noted. After thrombolysis patients were followed up till they leave the hospital. During the hospital stay they were closely monitored for development of complications like Heart failure, Cardiogenic shock, Arrhythmias, Thromboembolism and sudden cardiac death.

Diagnosis of STEMI was made by:

Presence of at least two of the following criteria:

1. Prolonged chest discomfort or angina equivalent (30 min)
2. Presence of more than or equal to 1 mm ST elevation in two consecutive leads.
3. Presence of elevated cardiac biomarkers.

ECG was interpreted as ST elevation in:

L1,aVL,V1-V6	:	Extensive anterior
L1,aVL	:	High lateral
L1,aVL,V5-6	:	Antero-Lateral
V1-V4	:	Anteroseptal
LII,LIII,aVF	:	Inferior
LII,LIII,aVF,rV4	:	Inferior+Right ventricular
LII,LIII,aVF,V8,V9	:	Inferior+Posterior

Diabetes mellitus:

Patients were considered as diabetic only when they were known diabetic on treatment or fasting blood sugar >126 mg%.

Hypertension:

Patients were considered hypertensive only when they were known hypertensive on treatment or Systolic BP>140mmHg and Diastolic BP>90mg%.

Central obesity:

Waist Hip Ratio	>1 for men
Waist Hip Ratio	>0.8 for women

Dyslipidemia:

Total cholesterol	>	240 mg%
LDL cholesterol	>	160 mg%
HDL cholesterol	<	40 mg%
Triglycerides	>	200 mg%

Serum Uric acid:

- Estimated by Uricase method**.**
- Considered elevated if serum level>7mg% for male, >6mg% for female.

All the above data were collected meticulously and entered into a proforma and master chart was prepared.

5.RESULTS AND OBSERVATIONS

Statistical method:

Data were analyzed using computer based SPSS 13.0 software by Chi – Square test. The p-value < 0.05 was considered as statistically significant.

Table 5.1:AGE & SEX DISTRIBUTION OF STUDY POPULATION

AGE	No. of Cases		
	Male	Female	Total
<40	10	2	12
41 – 50	18	16	34
51 – 60	20	15	35
61 – 70	7	7	14
>70	3	2	5
	58	42	100

Inference (Table 5.1):

The majority (69%) of the patients are between the age of 41-60. Males constitute 58% of study population. Females constitute 42% of study population.

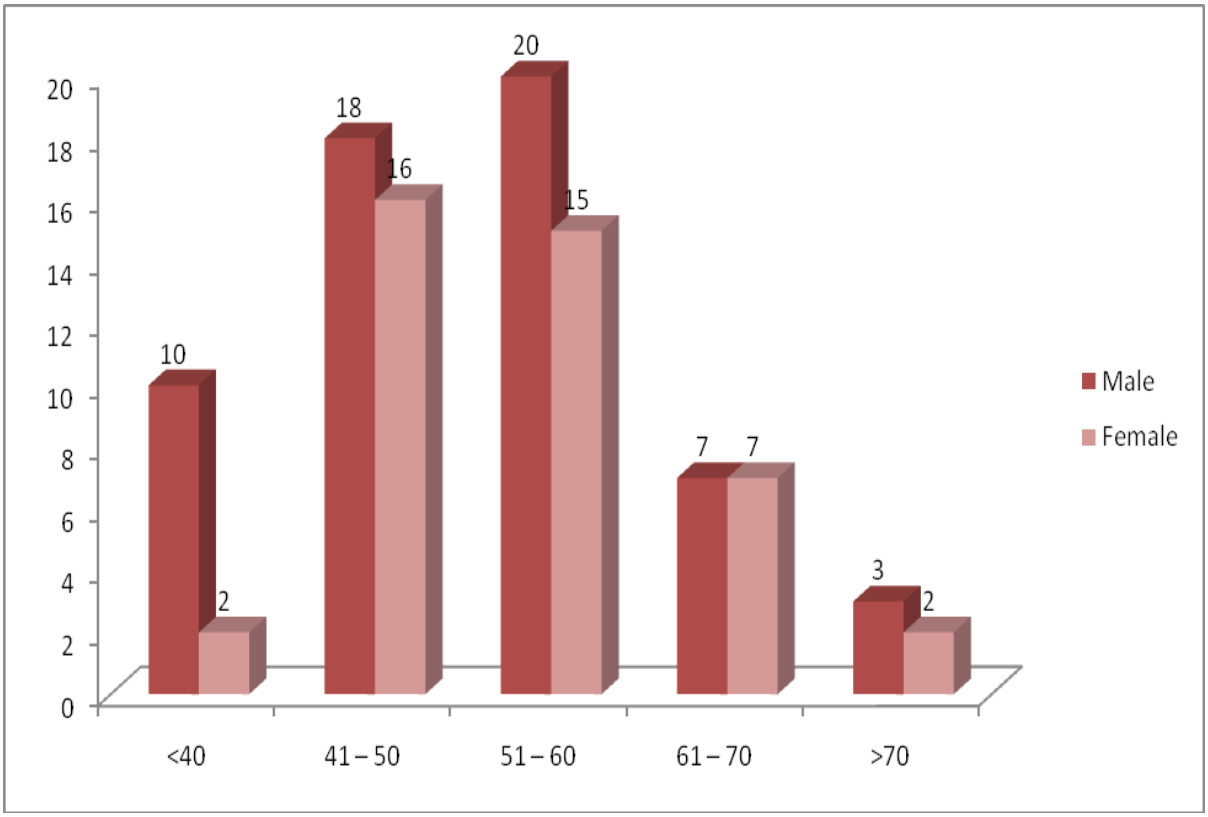

Fig. 5.1 Age and Sex Distribution of the study population

Table 5.2: Prevalence of Risk Factors

Sl. No	Risk Factors	No. of Cases	Percentage
1	Age > 50 years	54	54%
2	Smoking	29	29%
3	Alcoholism	21	21%
4	Diabetes Mellitus	51	51%
5	Hyper tension	36	36%
6	Central Obesity	46	46%
7	Dyslipidemia	41	41%
8	Hyperuricemia	30	30%

Inference(Table5.2):

Age > 50 years, Diabetes Mellitus &Central Obesity are the commonest risk factors. Hyperuricemia is present in 30% of study population.

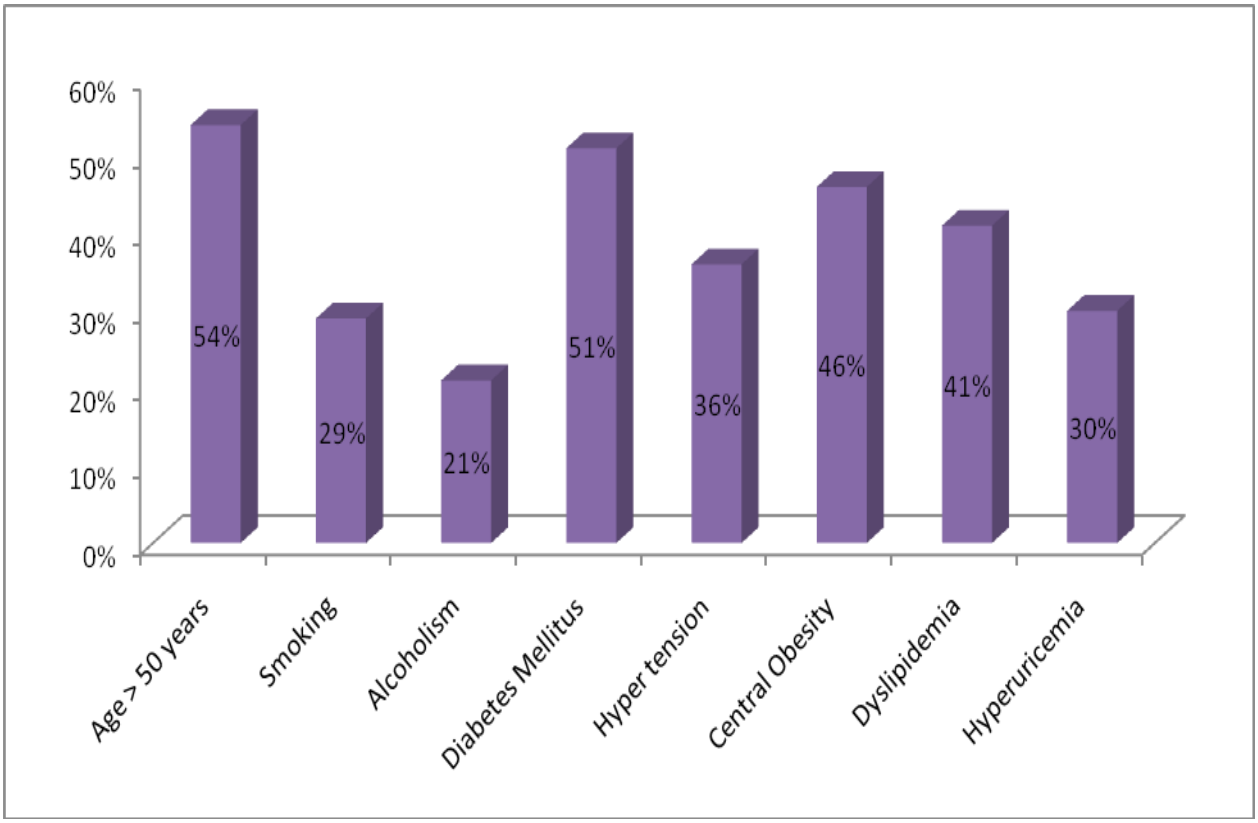

Fig. 5.2 Prevalence of Risk factors

Table 5.3: Distribution of Uric acid Values

	Lower Value	Higher Value	Mean	Standard Deviation
Male	2.8	8.1	6.141	1.287
Female	3.0	7.3	4.3	1.4836
Overall	2.8	8.1	5.368	1.6430

Inference (Table 5.3):

Mean Serum uric acid level in females is lower than males.

Table 5.4: Association of Individual Risk Factor with Hyperuricemia

Sl. No	Risk Factor	Hyper Uricemia		Risk Ratio	95% Confidence Interval	Chi - Square value	p - Value
		Yes	No				
1	Age > 50yrs	21	33	2.616	1.052 – 6.506	4.417	**0.029***
2	Smoking	10	19	1.342	0.533 – 3.381	0.391	0.346
3	Alcoholism	9	12	2.071	0.764 – 5.620	2.092	0.120
4	Diabetes Mellitus	21	30	3.111	1.248 – 7.753	6.191	**0.011***
5	Hyper Tension	16	20	2.857	1.179 – 6.923	5.589	**0.017***
6	Central Obesity	15	31	1.258	0.534 – 2.964	0.276	0.379
7	Dyslipidemia	12	29	1.156	0.394 – 2.253	0.018	0.537

Inference (Table 5.4):

Age > 50yrs, Diabetes Mellitus and Hypertension are the statistically significant risk factors associated with Hyperuricemia.

Table 5.5: Multivariate analysis of risk factors associated with Hyperuricemia

Variable	Co efficient	Std error	F – test	p – value
Age > 50 years	0.163	0.090	3.312	0.072
Male Sex	0.071	0.115	0.381	0.538
Smoking	-0.014	0.122	0.013	0.908
Alcoholism	0.201	0.120	2.7962	0.097
Diabetes Mellitus	0.260	0.089	8.5396	**0.004***
Hypertension	0.239	0.093	6.655	**0.011***
Central Obesity	0.141	0.098	2.0439	**0.036***
Dyslipidemia	0.031	0.099	0.098	0.753

Inference (Table 5.5):

While doing the Multivariate analysis, Diabetes Mellitus , Hypertension and Central obesity are the statistically significant risk factors associated with Hyperuricemia.

Table 5.6: Analysis of Association of Multiple Risk Factors& Hyperuricemia

No. of Risk Factors	Hyperuricemia		
	Yes	No	Total
5	3	1	4
4	14	9	23
3	12	16	28
2	2	31	33
1	0	11	11
Total	30	70	100

Chi-square -27.551; p-value: 0.001

Inference (Table 5.6):

The higher the number of total risk factors, the association with hyperuricemia becomes very significant.

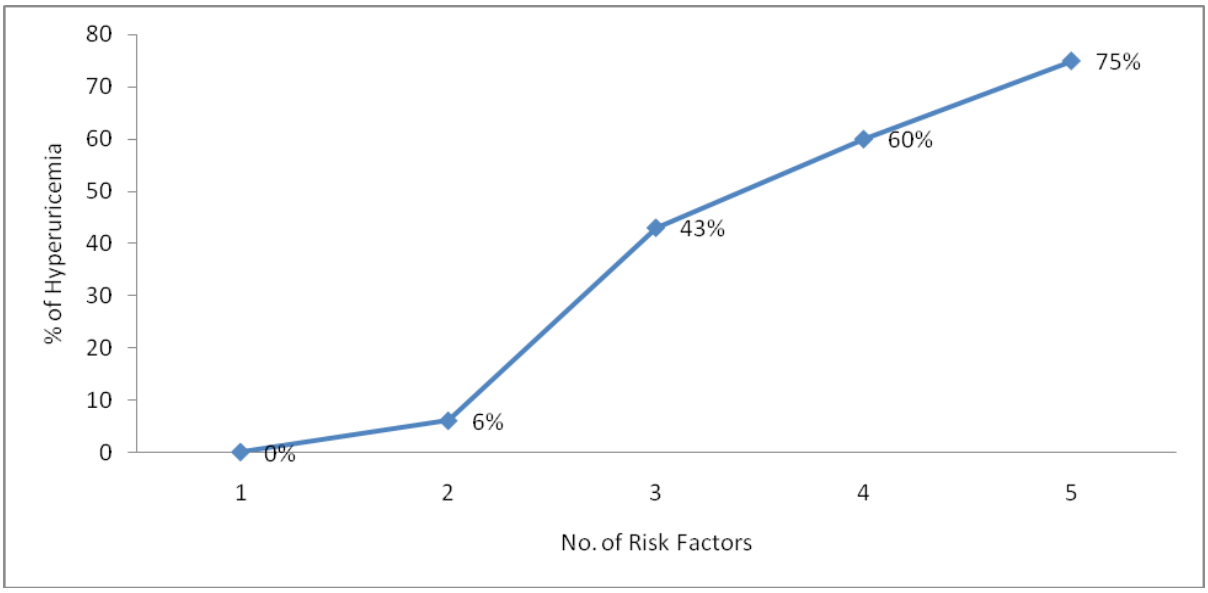

Fig 5.3 Association of Multiple Risk Factors& Hyperuricemia

Table 5.7: Multiple Risk Factors & Hyperuricemia

	Hyperuricemia		Risk Ratio	95% Confidence Interval	Chi-square Value	p – Value
	Yes	No				
Diabetes Mellitus	21	30	3.111	1.248 – 7.753	6.191	0.011*
Hyper Tension	16	20	2.857	1.179 – 6.923	5.589	0.017*
Age > 50yrs	21	33	2.616	1.052 – 6.506	4.417	0.029*
All the above factors together	8	5	**4.727**	1.399 –15.97	7.078	0.012*

Inference (Table 5.7):

While multiple risk factors are present in a single patient ,the probability of Hyperuricemia significantly rises .

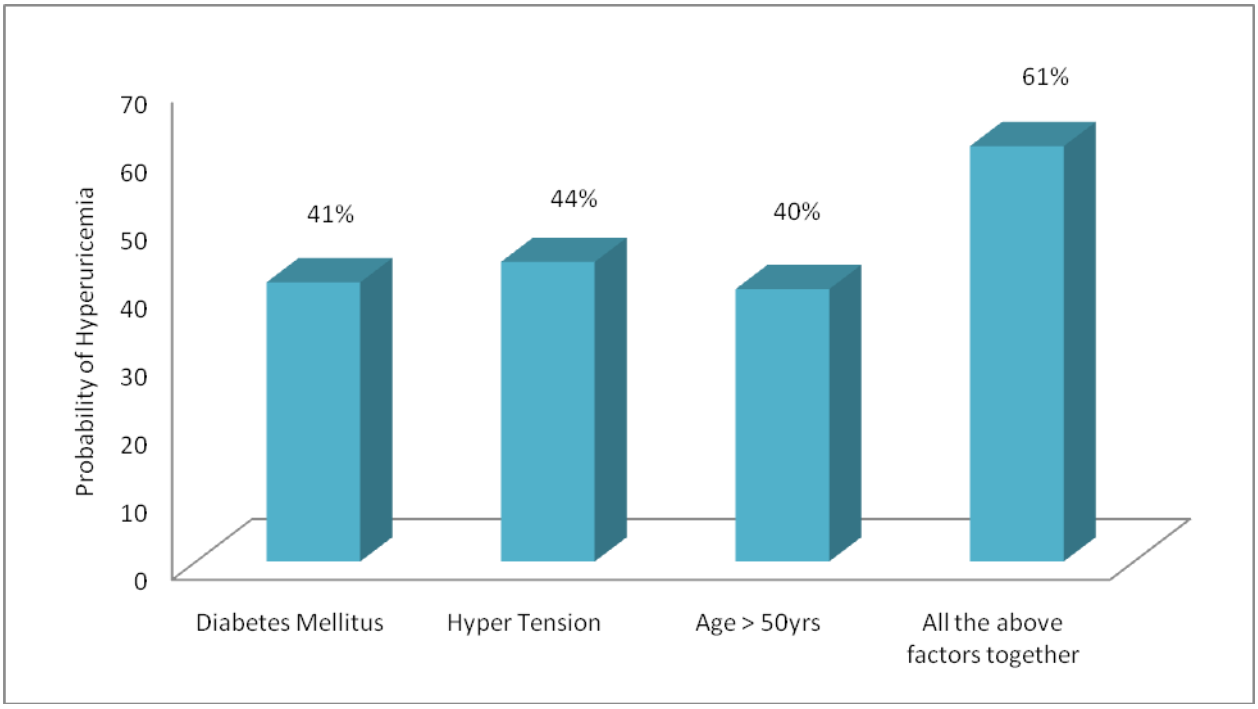

Fig 5.4 While Diabetes Mellitus, Hypertension, Age > 50 years are present in a single case risk of hyperuricemia increases by 50%

Table 5.8: Association of Hyperuricemia & Infarction Pattern

Type of Infarction	Hyperuricemia		Total
	Yes	No	
Anterior	25	32	57
Inferior	5	38	43
Total	30	70	100

Anterior = Anterolateral, ASMI & Extensive Anterior Wall

Inferior = IWMI, IWMI + PWMI, IWMI + PWMI + RVMI & IWMI + RVMI

Risk Ratio	95% Confidence Interval	Chisquare Value	p – Value
5.938	2.038 – 17.295	12.125	**0.001***

Inference (Table 5.8):

Anterior wall MI is significantly associated with Hyperuricemia.

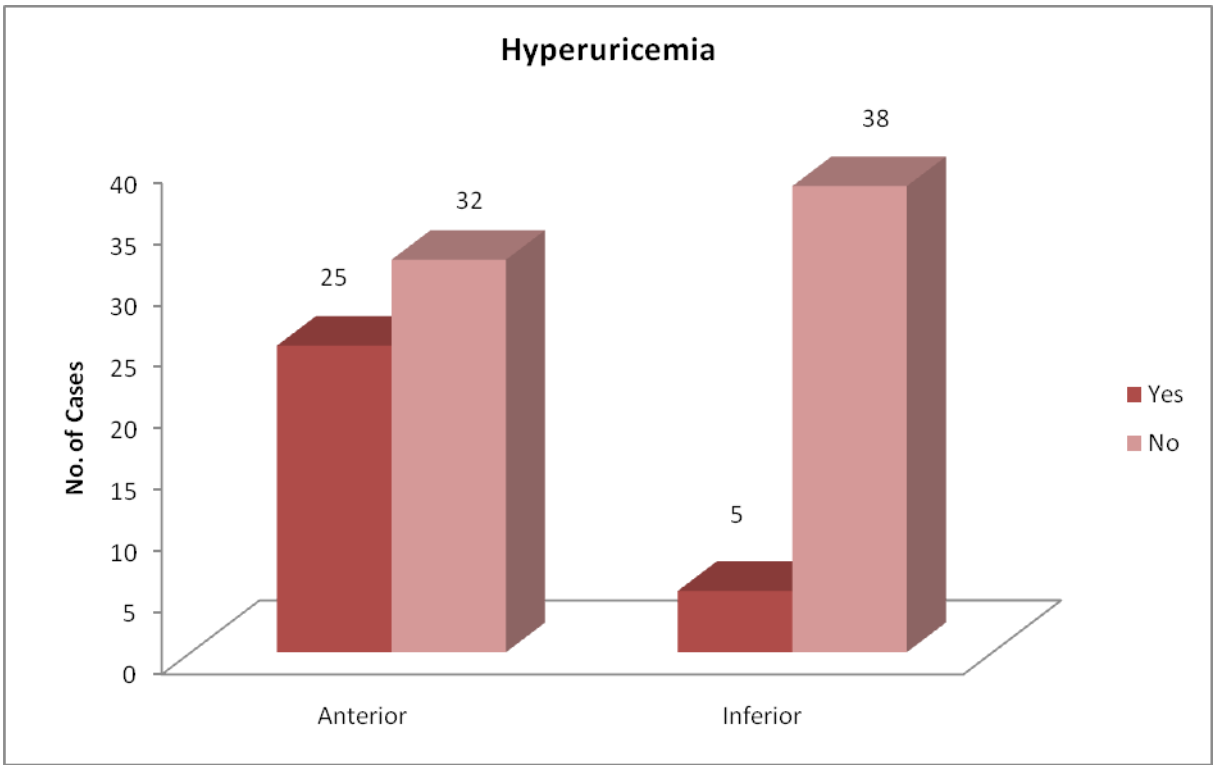

Fig 5.5 Anterior wall infarctions are more commonly associated with Hyperuricemia

Table 5.9: Pattern of Complications :(Total=32)

Sl. No	Complications	No. of Cases	Percentage
1	Cardiogenic Shock	14	44%
2	Arrhythmias	7	22%
3	Sudden Cardiac Death	8	25%
4	Cerebro vascular accident	3	9%
5	LV Aneurysm	0	0%
6	Ventricular septal rupture	0	0%
7	Ventricular free wall rupture	0	0%
8	Papillary muscle rupture	0	0%

Inference(Table 5.9):

Cardiogenic shock and arrhythmias are the common complications of STEMI. Other complications are sudden cardiac death and thromboembolism.

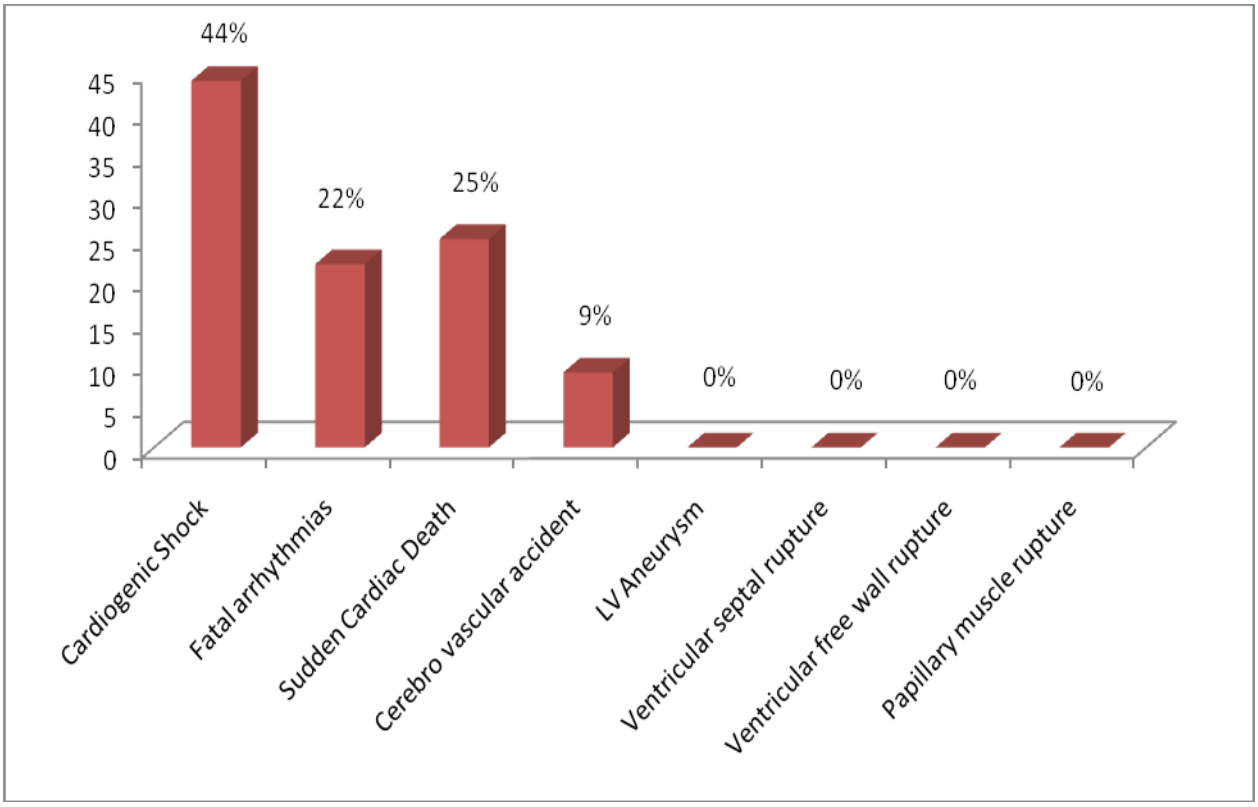

Fig 5.6 Pattern of Complications

Table 5.10: Association of Infarction type & Complications

Infarction Type	Complications		Total	Percentage
	Yes	No		
Anterior	23	34	57	57%
Inferior	9	34	43	43%

Anterior = Anterolateral, ASMI & Extensive Anterior Wall

Inferior = IWMI, IWMI + PWMI, IWMI + PWMI + RVMI & IWMI + RVMI

Inference Table(5.10):

STEMI involving anterior wall is significantly associated with more complications among the study population.

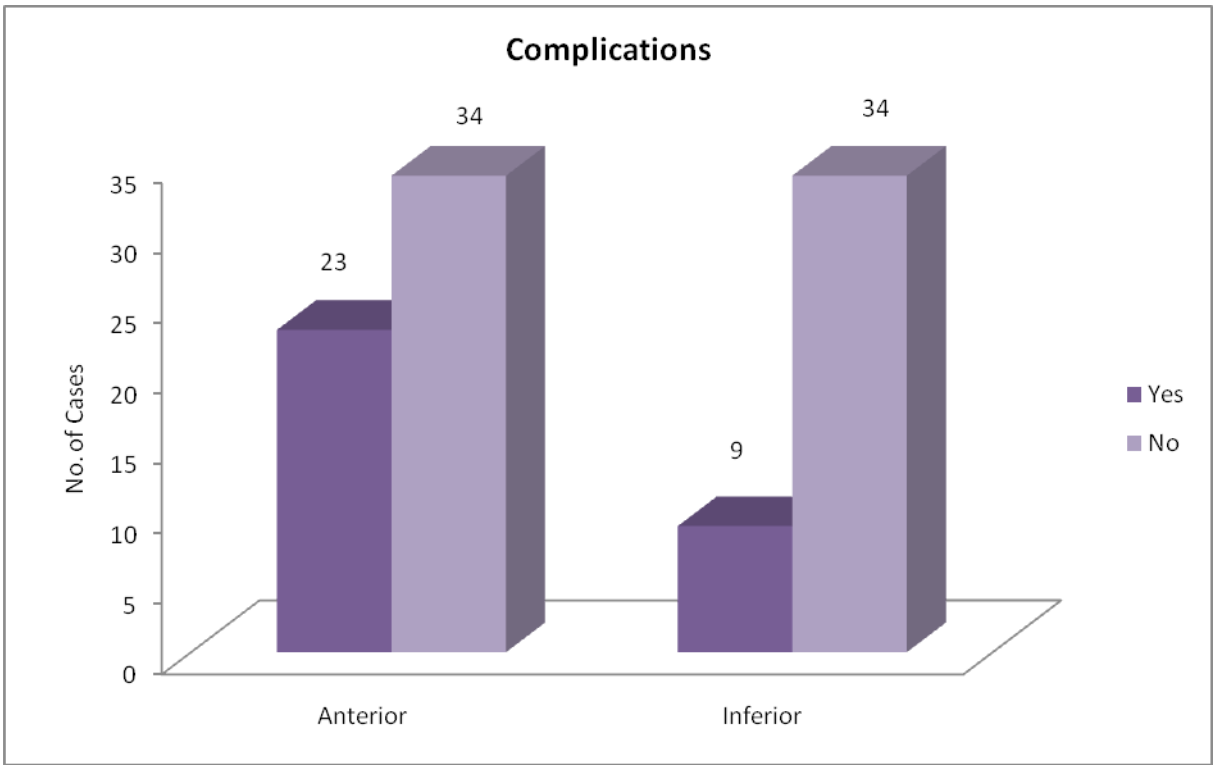

Fig 5.7 Anterior wall infarctions are more commonly associated with complications

Table 5.11: Multiple Risk Factor & Complications

	Complications		Risk Ratio	95% Confidence Interval	Chi-square Value	p - Value
	Yes	No				
Age > 50	25	29	4.803	1.828 – 12.621	11.026	0.001*
Hyperuricemia	17	13	4.795	1.910 – 12.038	11.984	0.001*
Diabetes Mellitus	21	30	2.418	1.011 – 5.787	4.028	0.036*
Dyslipidemia	18	23	2.516	1.064 – 5.947	4.524	0.026*
All the above factors together	7	1	**18.760**	2.196 – 160.256	12.309	0.001*

Inference (Table 5.11):

While multiple risk factors are present in a single patient ,the risk of complications significantly rises to several fold(four to five fold).

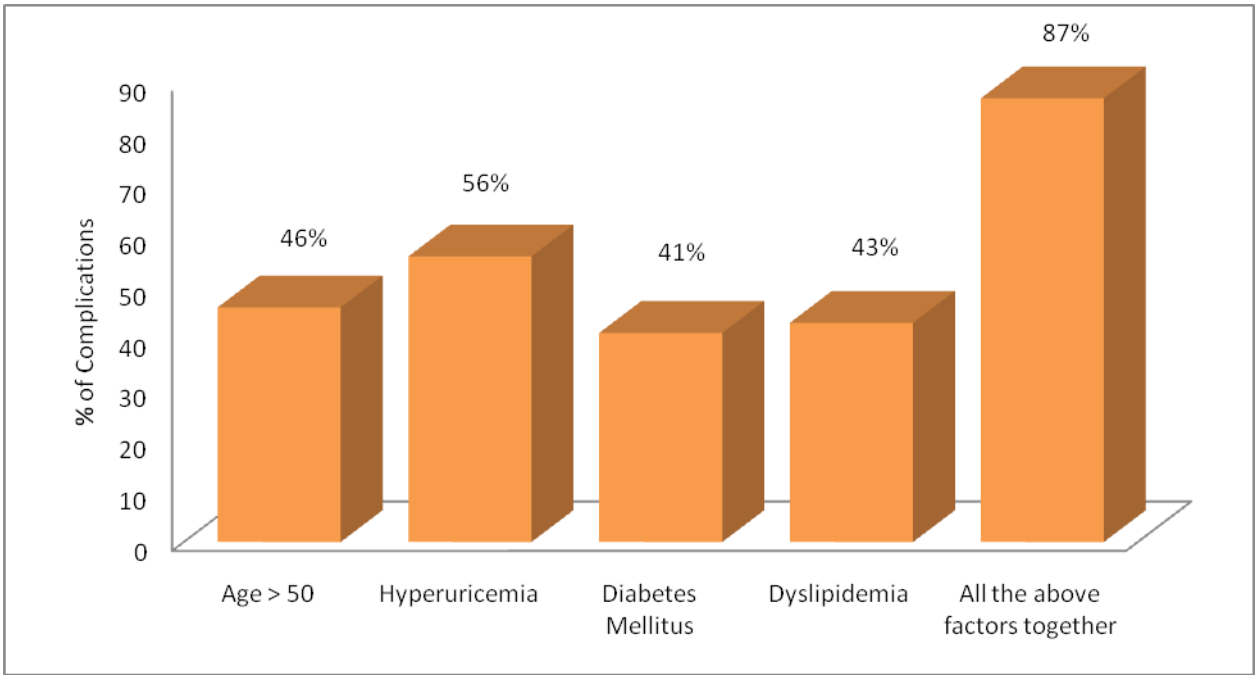

Fig 5.8 While Age >50, Hyperuricemia, Diabetes Mellitus and Dyslipidemia are present in a single case, there is a 100% raise in the possibility of complications.

Table 5.12: Association of Risk Factors (including Hyperuricemia) with Complications

SL No	Risk Factor	Compli-cations		Risk Ratio	95% Confidence Interval	Chi - Square value	p - Value
		Yes	No				
1	Age > 50	25	29	4.803	1.828 – 12.621	11.026	**0.001***
2	Dyslipidemia	18	23	2.516	1.064 – 5.947	4.524	**0.026***
3	Smoking	9	20	1.015	0.370 – 2.382	0.017	0.546
4	Alcoholism	8	13	1.410	0.517 – 3.844	0.454	0.335
5	Diabetes Mellitus	21	30	2.418	1.011 – 5.787	4.028	**0.036***
6	Hypertension	15	21	1.975	0.832 – 4.686	0.180	0.092
7	Central obesity	13	33	1.345	0.846 – 2.435	0.547	0.537
8	**Hyperuricemia**	17	13	4.795	1.910 – 12.038	11.984	**0.001***

Inference (Table 5.12):

Age > 50yrs, Diabetes Mellitus, Dyslipidemia and Hyperuricemia are the statistically significant risk factors associated with the complications in the study population.

Table 5.13: Multivariate analysis of risk factors for developing Complications

Variable	Co efficient	Std error	F – test	p – value
Age > 50 years	0.242	0.090	7.245	**0.008***
Male Sex	0.176	0.114	2.4125	0.123
Smoking	-0.088	0.120	0.533	0.466
Alcoholism	0.011	0.120	0.008	0.925
Diabetes Mellitus	0.113	0.092	1.528	0.219
Hypertension	0.098	0.095	1.064	0.304
Hyperuricemia	0.222	0.103	2.523	0.583

Inference(Table 5.13):

While doing the Multivariate analysis, only Age above 50 years is the statistically significant risk factor associated with the Complications.

6. DISCUSSION

In our study, male cases constitute 58% and female cases constitute 42%. Older age(age>50 years), Diabetes mellitus and central obesity are common risk factors associated with STEMI. Most of the patients with hyperuricemia are having more than one cardiovascular risk factors.

Several studies[21-25] demonstrated possible association of hyperuricemia with other cardiovascular risk factors and also with higher morbidity and mortality from Coronary artery diseases. Few studies[23] fail to reveal significant association between hyperuricemia and cardiovascular diseases.

However, our study shows statistically significant association of hyperuricemia with older age (Age>50years), Diabetes mellitus and hypertension through uni-variate analysis of cardiovascular risk factors. Multi-variate analysis reveals statistically significant association of hyperuricemia with Diabetes mellitus ,hypertension and central obesity.

In an Asian study[70] conducted by J. Woo, R. Swaminathan, C. Cockram, E. Lau' and A. Chan2,the association between serum uric acid concentration and some cardiovascular risk factors was examined in a working Hong Kong Chinese population (mean age 38 years), consisting of 910 men and 603 women. Positive associations were found between serum uric acid concentration and body mass index, waist hip ratio,

systolic and diastolic blood pressure, urea, creatinine, protein, glucose (fasting and 2 hours after 75 g oralglucose load), 2 hour insulin, triglycerides, and apolipoprotein B in men. In both sexes, serum uric acid was negatively associated with high-density lipoprotein cholesterol.

Moreover in our study, uni-variate analysis reveals statistically significant association of early complications of STEMI with Hyperuricemia and also with older age(Age>50years),Diabetes mellitus ,Dyslipidemia .

A large cross-sectional population-based study of epidemiological follow-up data from the First National Health and Nutrition Examination Survey[71] (NHANES I) from 1971-1975 and data from NHANES I Epidemiologic Follow-up Study (NHEFS) suggested that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality.

Another Asian study, the Japanese Acute Coronary Syndrome Study(JACSS)[72] conducted at Kumamato university also concluded that serum UA level after AMI is a good predictor of mortality in patients who have AMI.

7. CONCLUSIONS AND RECOMMENDATIONS

From the cross sectional study of "Serum uric acid in 100 patients with STEMI", conducted at Intensive Coronary Care Unit of Tirunelveli medical college Hospital, it is concluded that:

1. Mean Serum uric acid level is lower among females than males.
2. Hyperuricemia is statistically significantly associated with older age(Age>50years), Diabetes mellitus and hypertension.
3. Hyperuricemia becomes more prevalent while multiple cardiovascular risk factors are operating.
4. Hyperuricemia is statistically significantly associated with Anterior wall STEMI.
5. Hyperuricemia is statistically significantly associated with early complications of STEMI.

Recommendations:

1. Serum uric acid level can be used as a marker for assessing early complications of STEMI

2. However ,the measurement of Serum uric acid level does not replace the evaluation of other classical CHD risk factors but instead complements in assessing the early complications of STEMI.

3. Further large scale studies are needed with longer duration of follow up to establish the causal relationship of elevated Serum uric acid level with early complications of STEMI.

ABBREVIATIONS

ACS	-	Acute Coronary Syndrome
NSTEMI	-	Non ST Elevation Myocardial Infarction
STEMI	-	ST Elevation Myocardial Infarction
XO	-	Xanthine Oxidase
XDH	-	Xanthine Dehydrogenase
SUA	-	Serum Uric Acid
VSMC	-	Vascular Smooth Muscle Cell
NT-BNP	-	N – Terminal Brain Natriuretic Peptide
NCEP	-	National Cholesterol Education Programme.
NOS	-	Nitric Oxide Synthase
NO	-	Nitric Acid.
PDGF	-	Platelet Derived Growth Factor.
tHcy	-	Total Homocysteine
PAF	-	Platelet Activating Factor
VEGF	-	Vascular Endothelial Growth Factor
PECAM - 1	-	Platelet Endothelial Adhesion Molecule
VCAM - 1	-	Vascular Cell Adhesion Molecule
NHANES-I	-	First National Health and Nutrition Examination Survey
NHEFS I	-	NHANES I Epidemiologic Follow – up Study

PROFORMA

Name : Age: Sex: I.P.No :

Date of Admission : Date of Discharge :

Risk factors

Smoking :

Alcoholism :

Blood sugar :

Blood pressure :

Fasting lipid profile :

Serum uric acid :

Electrocardiogram :

Complications during hospital stay:

	Yes	No

1. Cardiogenic shock 2. Arrhythmias 3. Sudden cardiac death 4. Thrombo embolism 5. Ventricular aneurysm 6. Ventricular septal rupture 7. Ventricular Free wall rupture 8. Papillary muscle rupture		

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